

2/pyls

WO 00/57853

PCT/DE00/01028

Pharmaceutical Composition with An Extrusion Additive

This invention relates to pharmaceutical compositions that can be obtained by mixing at least one active ingredient with at least one extrusion additive from the group of polyalcohols esterified with fatty acids and joint melt extrusion.

The melt extrusion is a process that is known for the production of pharmaceutical compositions. In this case, very different adjuvants are used in the prior art for the various fields of application.

The melt extrusion process can be used universally per se, whereby, on the one hand, premixtures, which then can be further processed into the desired dosage forms, can be produced, or the desired dosage forms can be obtained directly by subsequent or simultaneous shaping.

In WO-9625151, the use of low-substituted water-insoluble hydroxypropylmethyl celluloses as additives in the case of the melt extrusion is described, by which the release of active ingredients can be set specifically.

DE-OS-4418837 thus describes a melt extrusion process that is suitable only for low-melting pharmaceutical active ingredients. According to this process, granulates that can be made into tablets directly are obtained, which then are further processed into the desired dosage forms.

09/937302-032700

The use of lipids in the production of solid dosage forms according to the melt extrusion process is also described in DE-OS-19531277. In this connection, the addition of lipids prevents the bonding of the mixture during the melt extrusion and subsequent form-calendering.

The known processes and preparations have, i.a., the drawback that a suitable or optimal extrusion process must be provided for almost any active ingredient. In this case, for example, what melting point the active ingredient has or whether it is in ionic form is to be noted.

To achieve an adequate release and "content uniformity" of low-dosed and poorly water-soluble active ingredients, a micronization can be performed. Micronized pharmaceutical substances have considerable drawbacks, however. In addition to the large amount of dust formed and the associated burden for the personnel, primarily a difficult handling based on air adsorption and relatively low densities can be mentioned. In addition, micronized pharmaceutical substances also often show the tendency to aggregate. Moreover, micronization is associated with high costs (devices, individual buildings).

Another process according to the prior art contains the use of organic solvents, whereby the pharmaceutical substance solution is sprayed on the adjuvants that are used. This has the

drawback that the necessary drying results in a thermal stress of the active ingredients. Disadvantageous ecological results when organic solvents are used are also given.

The object of this invention is therefore to provide a pharmaceutical composition that overcomes the drawbacks of the prior art.

The subject of this invention is therefore a pharmaceutical composition that can be obtained by mixing at least one active ingredient with at least one extrusion additive from the group of polyalcohols esterified with fatty acids and joint melt extrusion.

According to the invention, it is preferred that the extrusion additive be a sugar fatty acid ester, polyethylene glycol fatty acid ester or a glycerol fatty acid ester.

In this case, it is also preferred that the polyalcohols be diols, glycols, glycerol, mono-, di- or oligosaccharides, sugar alcohols, sorbitol, inositol, pentaerythritol, trimethylolpropane or polymer compounds with several hydroxy groups, polyalkylene glycols, polyethylene glycols, polyether polyols and polyester polyols and that the fatty acids have 1 to 31 carbon atoms and be unbranched and/or branched and/or saturated and/or unsaturated.

According to the invention, pharmaceutical compositions are also preferred in which as an additional adjuvant, polyvinylpyrrolidone, polyethylene glycol or vinylpyrrolidone-vinyl acetate-copolymer or a mixture of the above-mentioned substances is contained.

09937302-032702

The extrusion additives have a low melting point and/or their mixing with the active ingredient reduces the melting point in such a way that during the extrusion, the mixture does not have to be additionally heated but rather the compacting pressure in the extruder is sufficient to ensure the necessary temperature increase. It is therefore preferred that the melt extrusion be carried out without additional heat input.

The production of the extrusion additives is known in the art. They can be obtained by esterification of fatty acids with polyalcohols according to processes that are known in the art.

For esterification, suitable fatty acids are especially saturated, unbranched fatty acids, such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, palmitic acid, margaric acid, stearic acid, nonadecanoic acid, arachidic acid, behenic acid, lignoceric acid, cerotic acid, melissic acid, or saturated, branched fatty acids, such as isobutyric acid, isovaleric acid, tuberculostearic acid, or unsaturated, unbranched fatty acids, such as acrylic acid, crotonic acid, palmitoleic acid, oleic acid, erucic acid, sorbic acid, linoleic acid, linolenic acid, elaeostearic acid, arachidonic acid, clupanodonic acid, docosaheptaenoic acid.

For esterification, suitable polyols are organic compounds that contain at least two alcoholic hydroxy groups in the molecule, such as diols, glycols, glycerol, mono-, di- or oligosaccharides, such as glucose, galactose, mannose, fructose,

09937302-032702

arabinose, xylose, ribose, 2-deoxyribose, cellobiose, maltose, lactose, saccharose, gentiobiose, melibiose, trehalose, turanose, stachyose, acarbose, sugar alcohols, such as, for example, sorbitol and inositol, pentaerythritol, trimethylolpropane or polymer compounds, such as polyalkylene glycols, polyethylene glycols, polyether polyols and polyester polyols.

Subjects of the invention are pharmaceutical compositions with almost any active ingredients. Suitable active ingredients are, for example:

Acebutolol, acetylcysteine, acetylsalicylic acid, aciclovir, alprazolam, albumin, alfacalcidol, allantoin, allopurinol, ambroxol, amikacin, amiloride, aminoacetic acid, amiodarone, amitriptyline, amlodipine, amoxicillin, ampicillin, ascorbic acid, aspartame, astemizole, atenolol, beclometasone, benserazide, benzalkonium hydroxide, benzocaine, benzoic acid, betamethasone, bezafibrate, biotin, biperiden, bisoprolol, bromazepam, bromhexine, bromocriptine, budesonide, bufexamac, buflomedil, buspirone, caffeine, camphor, captopril, carbamazepine, carbidopa, carboplatin, cefaclor, cefalexin, cefadroxil, cefazolin, cefixime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime axetil, chloramphenicol, chlorhexidine, chloropheniramine, chlorthalidone, choline, ciclosporin, cilastatin, cimetidine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clavulanic acid, clomipramine, clonazepam, clonidine, clotrimazole, clozapine, codeine, colestyramine, cromoglycic acid, cyanocobalamin, cyproterone, desogestrel, dexamethasone, dexpanthenol, dextromethorphan,

09937302.032702

dextropropoxyphene, diazepam, diclofenac, digoxin, dihydrocodeine, dihydroergotamine, diltiazem, diphenhydramine, dipyrindamole, dipyrone, disopyramide, domperidone, dopamine, enalapril, ephedrine, epinephrine, ergocalciferol, ergotamine, erythromycin, estradiol, ethinylestradiol, etoposide, eucalyptus globulus, famotidine, felodipine, fenofibrate, fenoterol, fentanyl, flavin mononucleotide, fluconazole, flunarizine, fluorouracil, fluoxetine, flurbiprofen, furosemide, gemfibrozil, gentamicin, ginkgo biloba, glibenclamide, glipizide, glycyrrhiza glabra, guaifenesin, haloperidol, heparin, hyaluronic acid, hydrochlorothiazides, hydrocodone, hydrocortisone, hydromorphone, ipratropium hydroxide, ibuprofen, imipenem, indomethacin, iohexol, iopamidole, isosorbide dinitrate, isosorbide mononitrate, isotretinoin, ketotifen, ketoconazole, ketoprofen, ketorolac, labetalol, lactulose, lecithin, levocarnitine, levodopa, levoglutamide, levonorgestrel, levothyroxine, lidocaine, lipase, lisinopril, loperamide, lorazepam, lovastatin, medroxyprogesterone, menthol, methotrexate, methyl dopa, methylprednisolone, metoclopramide, metoprolol, miconazole, midazolam, minocycline, minoxidil, misoprostol, morphine, multivitamins and minerals, nystatin, N-methylephedrine, naftidrofuryl, naproxen, neomycin, nicardipine, nicergolines, nicotinamide, nicotine, nicotinic acid, nifedipine, nimodipine, nitrendipine, nizatidine, norethisterone, norfloxacin, norgestrel, nortriptyline, ofloxacin, omeprazole, ondansetron, pancreatin, panthenol, pantothenic acid, paracetamol, penicillin G, penicillin V, phenobarbital, pentoxifyllines, phenylephrine,

phenylpropanolamine, phenytoin, piroxicam, polymyxin B, povidone-iodine, pravastatin, prazosin, prednisolone, propafenone, propranolol, pseudoephedrine, pyridoxine, quinidine, ramipril, ranitidine, reserpine, retinol, riboflavin, rifampicin, rutoside, saccharin, salbutamol, salcatonin, salicylic acid, selegiline, simvastatin, somatropin, sotalol, spironolactone, sucralfate, sulbactam, sulfamethoxazole, sulpiride, tamoxifen, tegafur, teprenone, terazosin, terbutaline, terfenadine, theophylline, thiamin, ticlopidine, timolol, tranexamic acid, tretinoin, triamcinolone acetonide, triamterene, trimethoprim, troxerutin, uracil, valproic acid, vancomycin, verapamil, vitamin E, volic acid, zidovudine.

The pharmaceutical compositions according to the invention are solid dispersions that have a number of advantages per se. Such solid dispersions show, for example, an improved dissolution behavior, which is especially advantageous in the case of active ingredients that are sparingly soluble in aqueous media.

The pharmaceutical compositions according to the invention have a number of advantages. The composition has a high homogeneity, especially also for low-dosed active ingredients, whose content, for example, is less than 0.025% relative to the single dose. This is of major importance especially for low-dosed hormone preparations.

The active ingredients in the pharmaceutical compositions according to the invention also have a high "content uniformity," i.e., the deviation of the content of the single dose fluctuates only within lower limits. This is also of major advantage

00337302-032700

especially for low-dosed active ingredients. Pharmaceutical compositions according to the invention meet the boundary values that are required by the pharmacopeia (USP, Ph. Eur.).

Another advantage of the pharmaceutical compositions according to the invention is that the rate of solution in water of sparingly soluble active ingredients is significantly improved and a homogeneous distribution of the pharmaceutical substance is achieved without primarily treating the active ingredients.

The described invention thus represents an alternative, e.g., to micronization, whereby melt extrusion economically achieves the tasks set for it -- improving the rate of solution and achieving "content uniformity" -- in a single step.

Another advantage of the pharmaceutical compositions according to the invention is that the rate of solution of sparingly soluble active ingredients is significantly improved. Thus, such active ingredients can also be introduced into a preparation that again releases the active ingredient quickly and almost completely within a short time.

It is also advantageous if the mixture that is to be extruded already contains adjuvants that must no longer be added later as tablet adjuvants. Such extruded masses can then be further processed into tablets for example with a number of tablet adjuvants that is lower than the otherwise common number (e.g., elimination of lubricant).

It is also especially advantageous that thermolabile active ingredients in the pharmaceutical compositions according to the invention can also be processed. Since the extrusion additives

09937302.032702



are low-melting, if the additives are properly selected, external heating is often unnecessary. In any case, however, the procedure can be performed at low temperatures, for example 40 to 60°C.

Another subject of this invention is a process for the production of pharmaceutical compositions in which at least one active ingredient is mixed with at least one extrusion additive from the group of polyalcohols esterified with fatty acids, and the thus obtained mixture is then subjected to a common melt extrusion.

It is preferred according to the invention that the melt extrusion be carried out without heat input.

The amount of added extrusion additives is arbitrary per se. The optimal amount for the respective active ingredient is easy for one skilled in the art to determine with a few tests. The extrusion additives do not have any negative effects on the shelf life of the compositions, preparations and pharmaceutical agents that are produced with them. The extrusion additives are also well-tolerated since their degradation in the body (ester cleavage) results in not toxic, but rather generally physiological substances.

The pharmaceutical compositions that can be obtained according to the invention can be used directly as pharmaceutical agents. In this case, it may optionally be necessary to add additional pharmaceutically compatible adjuvants and additives to the mixture that consists of the active ingredients or the active ingredients with the extrusion additive or additives and then to

00937202-032702

subject this mixture to the melt extrusion. In this case, for example, form calenders can also be used to obtain the desired pharmaceutical agents.

Such pharmaceutical agents, however, can also be produced according to the invention in such a way that in addition the extruded mixture is ground and further processed into pharmaceutical agents with additional pharmaceutically compatible adjuvants and additives.

Subjects of this invention are thus also pharmaceutical agents that contain a pharmaceutical composition according to the invention together with other pharmaceutically compatible adjuvants and additives.

Another subject of this invention is also the use of polyalcohols that are esterified with fatty acids as extrusion additives for the production of pharmaceutical compositions according to the invention.

The following examples explain the invention:

Example 1:

Improvement of the Rate of Solution

Composition of a melt extrudate:

10% 17- $\beta$ -estradiol (not micronized)

50% PVP

40% saccharose-monopalmitate

The components are mixed. This mixture is subjected to a melt extrusion in a screw-type extruder with a one-hole nozzle at an extrusion temperature of 60°C and a screw speed of 50 rpm.

09937300 032702  
202200 0022660

The rate of solution is determined using dissolution tests (according to USP apparatus II) in 900 ml of 0.1N hydrochloric acid at 37°C over a period of 60 minutes (speed 100 rpm) and compared to that of the pure active ingredient and a physical mixture (Fig. 1).

The determination of the content of 17- $\beta$ -estradiol is carried out by HPLC. The detection is carried out by photometry at a wavelength of 242 nm.

Example 2:

Composition of a melt extrudate:

10% 17- $\beta$ -estradiol (not micronized)

50% vinyl pyrrolidone-vinyl acetate-copolymer

40% mixture that consists of PEG esters and glycerol esters

Extrusion temperature: 50°C; screw speed: 50 rpm

Example 3:

Composition of a melt extrudate:

30% 17- $\beta$ -estradiol (not micronized)

30% PEG 6000

40% saccharose monostearate and distearate

Extrusion temperature: 60°C; screw speed: 50 rpm

20220220E660

Example 4:

Improvement of the Rate of Solution of a Single Dose that Can Be Administered

Composition of a melt extrudate:

30% 17- $\beta$ -estradiol (not micronized)

30% PVP

40% saccharose-monopalmitate

Extrusion temperature: 60°C; screw speed: 50 rpm

The cooled melt extrudate is crushed and mixed in a mixer with tablet adjuvants.

Composition of a powder molding compound:

8.3% melt extrudate with 17- $\beta$ -estradiol

45.6% microcrystalline cellulose

45.6% corn starch

0.5% magnesium stearate

80 mg tablets with an active ingredient dose of 2 mg are produced on a tablet press.

The release rate is determined according to USP23-monography for estradiol tablets (Fig. 2). The contents of the samples are determined by HPLC with a photometric detection at 242 nm.

The requirements of the pharmacopeia on estradiol tablets with respect to the release are met.

09937302-032702  
20220820 09:26:00

## Example 5:

Use of a Lubricant as an Extrusion Additive

Composition of a melt extrudate:

30% 17- $\beta$ -estradiol (not micronized)

30% PVP

40% glycerol tribehenate

Extrusion temperature: 60°C; screw speed: 50 rpm

In the case of a subsequent tablet-making, the addition of a lubricant is no longer necessary.

## Example 6:

Achieving a Homogeneous Distribution of a Pharmaceutical Substance in a Vehicle ("Content Uniformity")

Composition of a melt extrudate:

10% ethinylestradiol (not micronized)

50% PVP

40% saccharose-monopalmitate

Extrusion temperature: 60°C; screw speed: 200 rpm

The study on "content uniformity" is carried out according to USP23. Tablets or solid dispersions at a dosage of 20  $\mu$ g in each case are studied. The examination of "content uniformity" is carried out using HPLC with a fluorimetric detection (Exc $\lambda$  = 281 nm; Em $\lambda$  = 305 nm).

The results correspond to the requirements of the USP. The variation coefficient in the examination on "content uniformity" lies significantly below the required 6%.

09937302-032702  
20220220E2E660

[Key to Figure 1:]

Comparison of the Rate of Solution of 17- $\beta$ -E2 to That of  
17- $\beta$ -E2 That Consists of a Melt Extrudate and a Physical Mixture

[First box:]

Composition of the melt extrudate  
and the physical mixture:

10% 17- $\beta$ -E2

50% PVP

40% saccharose monopalmitate

[Second box:]

17- $\beta$ -E2, untreated

melt-extruded solid

dispersion

physical mixture

17- $\beta$ -E2 freigesetzt [%] = 17- $\beta$ -E2, released [%]

[Key to Figure 2:]

Dissolution Test of a Tablet with a 17- $\beta$ -E2-Melt Extrudate

According to USP23

[Box:]

Composition of the solid dispersion:

30% 17- $\beta$ -E2

30% PVP

40% saccharose monopalmitate

17- $\beta$ -E2 freigesetzt [%] = 17- $\beta$ -E2, released [%]